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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,687	11/21/2001	Luisa Iruela-Arispe	1488.107000D/EKS/CML	9708

22195 7590 03/25/2005

HUMAN GENOME SCIENCES INC
INTELLECTUAL PROPERTY DEPT.
14200 SHADY GROVE ROAD
ROCKVILLE, MD 20850

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,687	IRUELA-ARISPE ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7 and 9-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7 and 9-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 4 and 8 have been canceled. Claims 1, 2, 5 and 6 have been amended. Claims 9-32 have been added. After review of the claims in light of the prior art, the species election requirement has been withdrawn. Claims 1-3, 5-7 and 9-32 are pending and under consideration.

The text of sections of Title 35, U.S. Code not found in this action can be found in a prior action.

Claims 1-3, 5-7, 13, 14, 25, 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3, 5-7 are drawn in part to methods which rely on the amino acid sequence encoded by the cDNA clone contained in ATCC 209581 and ATCC 209582.

The statement in the specification on page 3, lines 12-20 is insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met.

If deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a

statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:
(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:
(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:
(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
(d) the deposits will be replaced if they should become nonviable or non-replicable.
Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited cell lines are producing the polypeptides as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited cell lines are producing the polypeptides as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Claims 1-3, 5-7, 15-20 and 27-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5-7, 15-20 and 27-32 are drawn to methods reliant on a genus of METH1 and METH2 polypeptides which minimally comprise single domains of the METH polypeptides: a

polypeptide comprising the metalloprotease domain of METH1, amino acids 235 to 459 in SEQ ID NO:2; a polypeptide comprising the disintegrin domain of METH1, amino acids 460 to 544 in SEQ ID NO:2; a polypeptide comprising the first TSP-like domain of METH1, amino acids 545 to 598 in SEQ ID NO:2; a polypeptide comprising the second TSP-like domain of METH1, amino acids 841 to 894 in SEQ ID NO:2; a polypeptide comprising the third TSP-like domain of METH1, amino acids 895 to 934 in SEQ ID NO:2; a polypeptide comprising amino acids 536 to 613 in SEQ ID NO:2; a polypeptide comprising amino acids 549 to 563 in SEQ ID NO:2; a polypeptide comprising the metalloprotease domain of METH2, amino acids 214 to 439 in SEQ ID NO:4; a polypeptide comprising the disintegrin domain of METH2, amino acids 440 to 529 in SEQ ID NO:4; a polypeptide comprising the first TSP-like domain of METH2, amino acids 530 to 583 in SEQ ID NO:4; a polypeptide comprising the second TSP-like domain of METH2, amino acids 837 to 890 in SEQ ID NO:4; a polypeptide comprising amino acids 280 to 606 in SEQ ID NO:4; a polypeptide comprising amino acids 529 to 548 in SEQ ID NO:4.

The genus of polypeptides is highly variant because said polypeptide need only minimally comprise a fragments of SEQ ID NO:2 or 4. The claims do not limit the polypeptides by functional attributes. The specification provides a written description of SEQ ID NO:2, mature forms of SEQ ID NO:2, SEQ ID NO:4, mature forms of SEQ ID NO:4, and a variant of SEQ ID NO:4 having an additional 18 amino acids on the carboxyl terminus. This disclosure fails to adequately describe the claimed genus because the genus contains molecules which differ widely in structural attributes as well as functional attributes from SEQ ID NO:2 and 4. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus.

Claims 1 and 5 rejected under 35 U.S.C. 103(a) as being unpatentable over Klonowski et al (U.S. 6,649,377) in view of Kiyosuke et al (EP 742,012A2) or Fong et al (WO 99/14234).

Claims 1 and 5 are drawn in part to a method of treating an individual comprising administering an effective amount of a METH1 polypeptide comprising an amino acid sequence selected from the group consisting of amino acids 235-490, 545-598, 841-894, 895-934, 536-613 and 549-563 of the instant SEQ ID NO:4.

Klonowski et al teach that aggrecan is a major cartilage proteoglycan having a cleavage site between glutamic acid 373 and alanine 374 and that matrix metalloproteinase are unable to cleave at this site (column 1, lines 24-41). Klonowski et al teach that this site is cleaved by an endopeptidase called "aggrecanase" (column 1, lines 41-43) Klonowski et al teach the sequence of aggrecanase as Sequence Identifier 2 (Figure 1 and column 2, lines 42-47) which is identical to the instant SEQ ID NO:4 from residues 2-209, residues 211-532 and residues 534-950, thus fulfilling the structural requirements of amino acids 235-490, 545-598, 841-894, 895-934, 536-613 and 549-563 of the instant SEQ ID NO:4 as evidenced by the attached sequence alignment. Klonowski et al teach aggrecanase proteins that are substantially identical to the human aggrecanase protein, where by substantially identical is meant that the protein has an amino acid sequence identity to the sequence of aggrecanase of at least about 60%, usually at least about 65% and more usually at least about 70% (column 3, lines 53-58). The instant SEQ ID NO:4 has 78.6% identity to the aggrecanase of Klonowski et al .

Kiyosuke et al teach that diseases exhibiting pathosis of overproduction of an extracellular matrix, such as the postoperative scar, burn scar, keloid or hypertrophic scar remaining after a traffic accident, scleroderma, or arteriosclerosis are caused by abnormal overproduction of collagen which stimulates fibrosis resulting in the induration of the tissue to exhibit the disease pathology (page 2, lines 56-59). Kiyosuke et al teach that collagen synthesis plays an important role in diseases caused by vascularization, such as diabetic retinopathy, retrolental fibroplasia, vascularization due to corneal transplantation, glaucoma, eye tumor, trachoma, psoriasis, pyogenic granuloma, hemangioma, angiofibroma, hypertrophic scar, granulation, rheumatoid arthritis, scleredema, and atherosclerosis (page 3, lines 1-6).

Fong et al teach that an increment in myocardial mass as a result of an increase in myocyte size that is associated with an accumulation of interstitial collagen within the extracellular matrix and around intramyocardial coronary arteries has been described in left ventricular hypertrophy secondary to pressure overload in humans (page 2, lines 23-28). Fong et al teach that treatment of hypertension with diltiazem and captopril showed a decrease in left ventricular muscle mass, but the Doppler indices of diastolic function did not normalize and that this finding was attributed to excessive amounts of interstitial collagen which remain after regression of left ventricularhypertrophy (page 3, lines 23-27) .

It would have been prima facie obvious to use the instant METH1 polypeptide, comprising residues 235-490, 545-598, 841-894, 895-934, 536-613 and 549-563 in a method of treating diseases caused by collagen accumulation, such as those taught by Kiyoske et al and Fong et al. One of skill in the art would have been motivated to do so by the teachings of Klonowski et al on the activities of aggrecanase in cleaving collagen and the teachings of Klonowski et al on the structural requirements for an aggracanase variant.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
3/21/2005

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER